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Relationship of frontal lobe dysfunction and aberrant motor behaviors in patients with Alzheimer's disease

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ABSTRACT

Background: In order to address the neuropsychological pathogenesis of aberrant motor behaviors in Alzheimer's disease (AD), we used a cross-sectional study design to investigate the association between frontal lobe function, including executive function, and activity disturbances (wandering, purposeless activities and inappropriate activities).

Methods: Among 75 consecutive outpatients with AD, 50 subjects with a Clinical Dementia Rating (CDR) score of 1 or 2 were selected and divided into two groups based on data obtained from interviews with their caregivers: an aberrant motor behaviors (AMB) group (n = 22), and a non-aberrant motor behaviors (NAMB) group (n = 28). Aberrant motor behavior was defined according to whether the "activity disturbance" score (ranging from 0 to 9) of the Behavioral Pathology in Alzheimer Disease (Behave-AD) scale was 0 or ≥1. The total and subtest scores of the Frontal Assessment Battery (FAB) were then compared between the two groups.

Results: Significant differences were found between the FAB total ($P < 0.05$) and the subtest scores (lexical fluency, conflicting instructions; $P < 0.05$) in the two groups. The FAB score was significantly associated with the activity disturbance score ($r = -0.49$; $P<0.001$). A stepwise multiple regression analysis showed that only the FAB score significantly influenced the activity disturbance score ($P < 0.001$).

Conclusions: This finding suggested that in addition to episodic memory disturbance, frontal lobe dysfunctions might lead patients with AD to develop aberrant motor behavior.

Key words: Frontal Assessment Battery, dementia, activity disturbances, wandering, executive function

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is mainly characterized by episodic memory disorder, visuospatial impairment, attentional impairment, and executive dysfunction (Perry *et al.*, 2000; Baudic *et al.*, 2006). During the course of this disease, aberrant motor behaviors are reportedly observed as behavioral and psychological symptoms of dementia (BPSD) (Mega *et al.*, 1996; Devanand *et al.*, 1997).

The prevalence of aberrant motor behaviors is estimated to be in the range of 14–60% among patients with AD (Mega *et al.*, 1996; Devanand *et al.*, 1997; Liu *et al.*, 2004; Chiu *et al.*, 2006). On the other hand, the prevalence of aberrant motor behaviors among patients with frontotemporal lobar degeneration (FTLD) has been reported to be about 60–92% (Mendez *et al.*, 1998; Liu *et al.*, 2004; Chiu *et al.*, 2006).

Murman *et al.* (2002) reported that BPSD in patients with AD significantly increases the direct costs of care. In particular, aberrant motor behaviors in patients with dementia can create a distressful burden and cause suffering among caregivers, triggering or predicting nursing home placement (Donaldson *et al.*, 1997; Shinoda-Tagawa *et al.*, 2004; Scarmeas *et al.*, 2007). Thus, research on the etiology and treatment of these disturbances in patients with AD is urgently needed.

From a neuroanatomical aspect, the manifestation of aberrant motor behaviors in patients with neurodegenerative disease is associated with the right dorsal anterior cingulate cortex (dACC) and

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left premotor cortex in voxel-based morphometry (VBM) studies using magnetic resonance imaging (MRI) (Rosen *et al.*, 2005). However, a single-photon emission computed tomography (SPECT) study indicated that AD patients with wandering had a more severe decline in regional cerebral blood flow (rCBF) in the left parietal-temporal lobe (Rolland *et al.*, 2005).

From the neuropsychological perspective, previous studies have reported that behavioral problems or aberrant behaviors, such as wandering, purposeless activity and inappropriate activities, in patients with AD were significantly correlated with a decline in the Mini-mental State Examination (MMSE) score, which reflects global cognitive function (Folstein *et al.*, 1975; Devanand *et al.*, 1997; Harwood *et al.*, 2000). Moreover, in those studies, a positive correlation between the level of activities of daily living (ADL) and the severity of the aberrant motor behaviors in patients with AD was reported (Devanand *et al.*, 1997; Harwood *et al.*, 2000). Chiu *et al.* (2004) stated that behaviors that led to AD patients getting lost and beginning to wander might be caused not only by visuospatial impairments (O'Brien *et al.*, 2001), but also by executive and attentional dysfunction when navigating in unfamiliar environments. In another study, the severity and frequency of aberrant motor behaviors in patients with AD were associated with a decline in the scores of the behavioral assessment scale reflecting frontal lobe features (Engelborghs *et al.*, 2006).

For these reasons, the association between aberrant motor behaviors and cognitive impairment remains unclear, and the relationship between frontal lobe dysfunction and aberrant motor behavior is controversial. The Frontal Assessment Battery (FAB) is an easily administered test that can be completed at bedside within 10 minutes (Dubois *et al.*, 2000; Nakaaki *et al.*, 2007). Moreover, the FAB total and subtest scores differ significantly between FTLD and AD, but the MMSE scores do not; the ability of FAB to reflect frontal lobe function was previously confirmed in two studies examining different types of degenerative diseases (Slachevsky *et al.*, 2004; Lipton *et al.*, 2005). We previously reported that the manifestation of delusional thoughts in patients with AD was associated with a reduction in the FAB scores (Nagata *et al.*, 2009), reflecting executive function. However, the manifestation of aberrant motor behaviors has not been discussed as a cognitive aspect in conjunction with frontal lobe function. In the present cross-sectional study, we investigated the relationship between frontal lobe function and aberrant motor behavior using the FAB.

Methods

Participants

Seventy-five consecutive AD patients who had been referred to the Jikei University Kashiwa Hospital outpatient clinic were enrolled in this study. All the patients were diagnosed as having probable AD based on the National Institute of Neurology and Communicative Disorder and Stroke/Alzheimer Disease and Related Disorder Association (NINCDS/ADRDA) criteria (McKhann *et al.*, 1984). All diagnoses were made after an examination of the patients' past medical history, an evaluation of physical or neurological examinations, routine blood tests, and magnetic resonance imaging (MRI) findings by a geriatric psychiatrist (one of the four authors). The exclusion criteria were a history of alcohol or other substance abuse, brain injury, major depressive or psychotic disorder, epilepsy, delirium, metabolic disorder, or treatment with acetylcholine esterase inhibitor. Neuropsychological tests (FAB and MMSE) were administrated by a clinical psychologist. To determine the severity of each patient's dementia, the geriatric psychiatrists used the Clinical Dementia Rating scale (global CDR scores ranging from 0 to 3, where 0 = normal; 0.5 = questionable; 1 = mild; 2 = moderate; 3 = severe) (Hughes *et al.*, 1982) while interviewing each patient's caregiver. To recruit patients with mild- or moderate-stage AD, we selected patients (N = 50) with a global CDR score of either 1 or 2. Patients with a global CDR score of either 0.5 or 3 were excluded from this study. The patients were divided into two groups: an aberrant motor behaviors (AMB) group, and a non-aberrant motor behaviors (NAMB) group. The manifestation of aberrant motor behavior was assessed based on information obtained from a structured interview with each patient's caregiver by the same geriatric psychiatrists, and the aberrant motor behaviors were rated using the "activity disturbance" score of the Behavioral Pathology in Alzheimer's Disease (Behave-AD) scale (Reisberg *et al.*, 1987). The four geriatric psychiatrists and clinical psychologist were experienced at performing neuropsychological and behavioral examinations, and the inter-rater validity of the scales was sustained by periodic discussions and exchanges of views. This study was approved by the Ethics Committee of the Jikei University School of Medicine.

Definition of aberrant motor behaviors

To determine whether the patients had aberrant motor behaviors, we used the activity disturbance scale of the Behave-AD (total behavioral or

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psychological problems scale). This scale was completed based on the results of an interview with each patient's caregiver, who was asked whether the patient had experienced any of the following aberrant motor behaviors in the previous four weeks: (1) "wandering away from home or caregivers", (2) "purposeless activity", and (3) "inappropriate activity" (Reisberg *et al.*, 1987). The severity range of each score was from 0 to 3, and the range of the total activity disturbance score was from 0 (not present) to 9 points. If the total score was ≥1 point, the patient was classified in the aberrant motor behaviors (AMB) group. If the total score was 0, the patient was classified in the non-aberrant motor behaviors (NAMB) group.

FAB assessment

The Japanese FAB version consists of six subtests: (1) similarities (conceptualization); (2) lexical fluency (mental flexibility); (3) motor series (programming); (4) conflicting instructions (sensitivity to interference); (5) go – no go (inhibition control); and (6) prehension behavior (environmental autonomy) (Takagi *et al.*, 2002). Each subtest was rated from 3 to 0, with the total score ranging from 18 to 0.

Statistical analysis

SPSS 16.0J for Windows (SPSS Japan Inc) was used for all statistical analyses. To compare differences between the two groups, we used a one-way ANOVA with post-hoc testing for age, education (years), duration of illness (months), the MMSE total score, the CDR Scale sum of boxes (CDR SB: ranging from 0 to 18), the FAB total score, and the FAB subtest scores. The sex ratio (female to male) was assessed using a χ^2 test. Other behavioral or psychological problems (delusion, hallucination, and anxiety score of the Behave-AD subscale) were compared between the two groups using a one-way ANOVA with Tukey post-hoc test. Pearson correlation coefficients were used to evaluate the associations between FAB or MMSE and the activity disturbance score (ranging from 0 to 9). Finally, a stepwise multiple regression analysis was performed to examine the contribution of age, sex, education, duration of illness, FAB total score, MMSE score and CDR SB score as independent variables of the activity disturbance score. A p value <0.05 was considered statistically significant.

Results

Patient characteristics

Fifty AD patients (11 males and 39 females; average age, 78.2 ± 7.1 years; range, 59–91 years) were classified as belonging to either the AMB group (n = 22) or the NAMB group (n = 28). These two groups were not significantly different with regard to the sex ratio ($\chi^2 = 1.601$; $df = 1$; $P = 0.206$), age ($F = 1.483$; $df = 1$; $P = 0.229$), duration of illness (months) ($F = 0.421$; $df = 1$; $P = 0.405$), education (years) ($F = 0.704$; $df = 1$; $P = 0.519$), MMSE score ($F = 3.350$; $df = 1$; $P = 0.074$), or CDR SB score ($F = 3.271$; $df = 1$; $P = 0.077$). However, the FAB total scores ($F = 7.044$; $df = 1$; $P = 0.011$) were significantly different between the two groups (Table 1). The mean ± standard deviations (SDs) of the FAB scores were 12.3 ± 3.3 (NAMB) and 9.3 ± 4.5 (AMB). The two subscores of the FAB, lexical fluency ($F = 6.390$; $df = 1$; $P = 0.015$) and conflicting instructions ($F = 5.469$; $df = 1$; $P = 0.024$), were both significantly lower in the AMB group than in the NAMB group (Table 2). The mean ± SDs of the lexical fluency scores were 1.86 ± 1.01 (NAMB) and 1.10±1.09 (AMB), while those of the conflicting instrument scores were 2.71±0.53 (NAMB) and 2.10±1.26 (AMB).

Table 1. Subject characteristics (mean ± SD)

GROUP	AMB (n = 22) (MEAN ± SD)	NAMB (n = 28) (MEAN ± SD)	χ^2 OR F SCORE	P VALUE
Sex (male/female)	3/19	8/20	1.601	0.206
Age	79.5 ± 6.6	77.1 ± 7.3	1.483	0.229
Education (years)	10.8 ± 3.4	11.6 ± 2.5	0.421	0.519
Duration of illness (months)	28.7 ± 18.3	24.2 ± 19.3	0.704	0.405
MMSE score	18.2 ± 5.3	20.3 ± 2.8	3.35	0.074
FAB score	9.3 ± 4.5	12.3 ± 3.3	7.044	0.011*
CDR SB	8.18 ± 3.20	6.80 ± 2.17	3.271	0.077

AMB = aberrant motor behavior, NAMB = non-aberrant motor behavior; CDR SB = Clinical Dementia Rating Scale sum of boxes (ranging from 0 to 18).
*$P<0.05$ (ANOVA with post-hoc test).
The sex ratio was analyzed using the χ^2 test.

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Table 2. FAB subtest scores (mean ± SD)

SUBTEST	AMB (n = 22) (MEAN ± SD)	NAMB (n = 28) (MEAN ± SD)	*F* SCORE	*P* VALUE
Similarities	1.00 ± 0.95	1.25 ± 1.17	0.638	0.428
Lexical fluency	1.10 ± 1.09	1.86 ± 1.01	6.39	0.015*
Motor series	1.57 ± 1.25	2.04 ± 1.17	1.785	0.188
Conflicting instructions	2.10 ± 1.26	2.71 ± 0.53	5.469	0.024*
Go-no go	1.14 ± 1.24	1.61 ± 1.10	1.922	0.172
Prehension behavior	2.38 ± 1.02	2.82 ± 0.48	4.044	0.05

AMB = aberrant motor behavior; NAMB = non-aberrant motor behavior.
*$P<0.05$ (ANOVA with post-hoc test).

Table 3. Stepwise multiple regression analysis for activity disturbance scores of Behave-AD

VARIABLE	B	SE	β	t value	P VALUE
Constant	2.856	0.512		5.577	P<0.001
FAB	−0.18	0.43	−0.522	−4.156	P<0.001

Stepwise multiple regression analysis of FAB score, age, sex, education, duration of illness, MMSE score, and CDR sum of boxes for activity disturbance scores (N = 50).
B = partial regression coefficient; SE = standard error; β = standardized partial regression coefficient.
$R = 0.522$, $R^2 = 0.273$.

Other behavioral and psychological problems including delusion, hallucination and anxiety in the two groups

We also compared other behavioral and psychological problems that might have influenced the aberrant motor behaviors between the AMB group and the NAMB group. The two groups were not significantly different with regard to the delusion score ($F = 0.473$; $df = 1$; $P = 0.495$), the hallucination score ($F = 1.874$; $df = 1$; $P = 0.177$), or the anxiety score ($F = 2.016$; $df = 1$; $P = 0.162$) of the Behave-AD subscales.

Contribution of age, sex, education, duration of illness, FAB total scores, MMSE scores and CDR sum of boxes scores to the severity of aberrant motor behaviors

The FAB score was significantly correlated with the activity disturbance score ($r = -0.490$; $P<0.001$) and the MMSE score ($r = 0.670$; $P<0.001$). The MMSE score was also significantly correlated with the activity disturbance score ($r = -0.317$; $P<0.001$). A stepwise regression analysis showed that the FAB score significantly affected the activity disturbance score ($P<0.001$; $R^2 = 0.273$) (Table 3).

Subtypes of aberrant motor behaviors

Although 22 patients had experienced aberrant motor behaviors, several types overlapped in one patient. Purposeless activity (e.g. opening and closing a pocketbook, packing and unpacking clothing, repeatedly putting on and removing clothing, insistently repeating demands or questions) was the most frequently reported aberrant motor behavior (N = 15). Inappropriate activity (e.g. storing and hiding objects in inappropriate places, throwing clothing in a waste basket or putting empty plates in the oven; inappropriate sexual behaviors such as inappropriate exposure) was reported in 13 patients, while wandering was reported in three patients.

Discussion

The results indicate that the FAB total score in patients with AD was significantly related to the presence of aberrant motor behaviors. While the MMSE total score reflects global cognitive function weighted on orientation and memory function (Folstein *et al.*, 1975), the FAB has been confirmed to reflect executive function and working memory in patients with FTLD (Dubois *et al.*, 2000; Nakaaki *et al.*, 2007). Moreover, the FAB total and subtest scores significantly differ between FTLD and AD, emphasizing the validity of using the FAB to reflect frontal lobe function (Slachevsky *et al.*, 2004; Lipton *et al.*, 2005; Nakaaki *et al.*, 2007). The FAB was also shown to be a valid frontal function test in a SPECT study (Yoshida *et al.*, 2009), with a positive correlation observed between the left callosomarginal and precentral rCBF.

Some previous studies have reported that global cognitive and functional impairments in AD patients are associated with several BPSD, including aberrant motor behaviors (Mega *et al.*, 1996; Devanand *et al.*, 1997; Harwood *et al.*, 2000). Although some studies have indicated that aberrant motor behaviors are associated with cognitive or ADL decrements, only a few studies

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have indicated an association between frontal lobe function and aberrant motor behavior (Swanberg *et al.*, 2004; Engelborghs *et al.*, 2006). In the present study, the activity disturbances score was significantly correlated with the MMSE score ($r = -0.317$; $P<0.001$), but a stronger correlation ($r = -0.490$; $P<0.001$) and association with the FAB was revealed using a statistical regression analysis. Among several aspects of neurocognitive dysfunction, we were particularly interested in the association between frontal lobe dysfunction and aberrant motor behavior from a neuropsychological aspect.

The FAB subtests (lexical fluency, conflicting instructions) were significantly lower in AD patients with aberrant motor behavior. Dubois *et al.* (2000) described that in the lexical fluency task, patients needed the ability to recall as many words as possible starting with a given letter within a limited number of seconds. Such literal fluency tasks also require self-organized retrieval from semantic memory and flexible behavioral adaptations to new situations (Dubois *et al.*, 2000). Therefore, the aberrant motor behaviors, including wandering or inappropriate activity, might be caused by an inability to react flexibly with variable stimuli in their environment. The conflicting instruments subtest resembles the Stroop test task and requires the ability to perform a contrary reaction to each of two pattern directions effectively (Dubois *et al.*, 2000). In patients with AD, in addition to memory disorders and visuospatial impairments, the lack of such self-correction in executive functions might particularly cause impairments in their ability to carry out these tasks efficiently, leading to wandering, inappropriate activity or purposeless activity resembling stereotypical behaviors as a result. Moreover, several studies have reported associations between each subtest and specific regions of frontal lobes using various neuroimaging methods. For example, functional magnetic resonance imaging (fMRI) or position emission tomography (PET) studies have reported an association between lexical fluency and the medial frontal cortex, including the anterior cingulate gyrus (Waburton *et al.*, 1996; Crosson *et al.*, 1999) and between the conflicting instruments and the right orbito-frontal and anterior cingulate cortex (Bench *et al.*, 1993). These reports partially support the results of a previous voxel-based morphometry study in patients with neurodegenerative disease and might imply an association between the anterior cingulate cortex and the aberrant motor behaviors (Rosen *et al.*, 2005).

In the present study, among the 22 AD patients (44%) with aberrant motor behaviors, only three exhibited wandering, 15 exhibited purposeless activity, and 13 exhibited inappropriate activity. Previous studies have shown that the prevalence of aberrant motor behaviors in patients with mild- or moderate-stage AD ranges from about 12% to 67% (Mega *et al.*, 1996; Devanand *et al.*, 1997), similar to our reported data. Schonfeld *et al.* (2007) also showed that wandering in nursing homes was frequently (21%) observed in patients with severe cognitive impairments.

The present study has some limitations. First we must consider the relatively small sample size and the lack of objective measures, with only two neuropsychological assessments – the FAB and the MMSE – being performed. In particular, the subjects with wandering might have a high risk of visuospatial memory or perception impairments leading to "getting lost" (Chiu *et al.*, 2004). Secondly, the present study was limited to subjects with mild- to moderate-stage AD whose CDR scores were 1 or 2, because even though the FAB tasks can be performed without tools or instruments, the tasks do contain relatively complex question forms that include several steps. Thirdly, apraxia symptoms as focal signs of AD should be quantitatively assessed, as subjects with severe ideational apraxia cannot carry out sequences of action to achieve an intended purpose in the correct order (Zadikoff *et al.*, 2005). Fourthly, because the FAB score was significantly correlated with the MMSE score ($r = 0.670$; $P<0.001$), we might have used two relevant neuropsychological tests. Therefore, we confirmed that the activity disturbances score was more strongly associated with the FAB score than with the MMSE score or the CDR SB using a stepwise regression analysis. Finally, this study had a cross-sectional design, and significant associations with other BPSD symptoms (delusional ideation, hallucination and anxiety) were not observed. If the clinical courses of the patients were to be pursued longitudinally, another BPSD symptom might be added, resulting in a worsening of the aberrant motor behaviors.

In spite of these limitations, the present study supported the hypothesis that frontal lobe dysfunction might be related to aberrant motor behaviors in patients with AD, supporting the results of neuroimaging studies. Moreover, these results suggest that a simple neuropsychological screening test reflecting frontal lobe function and including mainly executive function – such as the FAB – might be useful for predicting the manifestation of aberrant motor behaviors in patients with AD, providing important information regarding the selection of treatment stages that might reduce the early burden placed on caregivers.

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Conflict of interest

None.

Description of authors' roles

Tomoyuki Nagata designed this study, examined the subjects, and wrote the paper. Shunichiro Shinagawa gave advice, including the analysis methods, and reviewed the manuscript. Hirohide Kada, Yusuke Ochiai and Hiroo Kasahara examined the patients with AD at the Jikei University School of Medicine, Kashiwa Hospital. Kazutaka Nukariya and Kazuhiko Nakayama reviewed and commented on the final manuscript.

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